85. (New) The host-vector system of claim 84, wherein the suitable host cell is E. coli.

86. (New) The host-vector system of claim 84, wherein the suitable host cell is a COS cell.

87. (New) The host-vector system of claim 84, wherein the suitable host cell is a CHO cell.

88. (New) A method of producing a fusion polypeptide which comprises growing cells of the host-vector system of claim 83, under conditions permitting production of the fusion polypeptide and recovering the polypeptide so produced.--

Support for new claims 42-88 can be found throughout the specification.

In the specification

On page 1, line 3, before "This", please insert the following claim priority data:

This application is a U.S. National Stage Application of PCT International Application No. PCT/US99/30900, filed December 23, 1999, which claims priority to U.S. Provisional Application No. 60/113,387, filed December 23, 1998, now abandoned.

REMARKS

Attached herewith as Exhibit A are marked up copies of the amended pages and as Exhibit B are substitute sheets of the amended pages.

Applicants have canceled claims 1-41 and replaced them with new claims 42-88. Therefore, Applicants will consider new claims 42-88 for the purpose of calculating the filing fees associated with the U.S. National Stage Application filed concurrently herewith. No fee is deemed necessary in connection with filing this Preliminary Amendment. However, if any fee is deemed necessary,

authorization is hereby given to charge the amount of any such fee to Deposit Account No. 18-0650.

Respectfully submitted,

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METHOD OF ENHANCING THE BIOLOGICAL ACTIVITY OF LIGANDS

This application is a U.S. National Stage application of PCT International application No. PCT/US99/30900, filed December 23, 1999, which ~~This application~~ claims priority of U.S. Application No. 60/113,387, filed December 23, 1998. Throughout this application, various publications are cited. The disclosures of each and all of those publications are hereby incorporated by reference in their entireties into this application.

INTRODUCTION

The present invention provides for novel methods for producing novel fusion polypeptide ligands that have enhanced biological activity as compared to the polypeptide ligands in their native form. The invention also provides for nucleic acids useful for producing biologically active fusion polypeptide ligands, and the fusion polypeptide ligands themselves.

BACKGROUND OF THE INVENTION

The ability of polypeptide ligands to bind cells and thereby elicit a phenotypic response such as cell growth, survival or differentiation is often mediated through transmembrane tyrosine kinases. The extracellular portion of each receptor tyrosine kinase (RTK) is generally the most distinctive portion of the molecule, as it provides the protein with its ligand-recognizing characteristic. Binding of a ligand to the extracellular domain results in signal transduction via an intracellular tyrosine kinase catalytic domain which transmits a biological signal to intracellular target proteins. The particular array of sequence motifs of this cytoplasmic, catalytic domain determines its access to potential kinase substrates (Mohammadi, et al.,1990, Mol. Cell. Biol., 11: 5068-5078; Fantl, et al., 1992, Cell, 69:413-413).

RTKs appear to undergo dimerization or some related conformational change following ligand binding (Schlessinger, J., 1988, Trend Biochem. Sci.